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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/611,902	07/03/2003	Hiroshi Takeyama	Q76104	8672

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
12/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/611,902	TAKEYAMA ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 16-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3 and 16-17 are presented for examination

Applicants' amendment filed 10/15/2007 has been received and entered into the application. Accordingly, claim 1 has been amended.

Applicants' arguments, filed 10/15/2007, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In light of the new rejections being applied against the pending claims, this Office Action is **Non-Final**.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

Interview Summary

In response to Applicants' Summary of Interview with Examiner as filed on 10/15/2007, the Examiner would like to clarify that when he indicated in the interview that favorable consideration would be given to claims limited to stomach tumors, he did not mean that he would "likely consider claim 1 to be allowable" if claim 1 were limited to stomach tumors as

suggested in Applicants' Interview Summary on page 3. Please refer to the Examiner Interview Summary Record mailed 10/10/2007.

Response to Arguments

Applicants' arguments, see Response, filed 10/15/2007, with respect to the combination of Casciari *et al.* in view of PP-1457 and Stedman's Medical Dictionary have been fully considered and are persuasive. Casciari *et al.* is drawn solely to the combination of lipoic acid and vitamin C. There is no suggestion that lipoic acid could be substituted with the claimed benzyl alcohol. The rejection of claims 1-3 and 16-17 over Casciari *et al.* in view of PP-1457 and Stedman's Medical Dictionary has been withdrawn.

However, with respect to Applicants' arguments of unexpected results, after careful consideration of the 37 C.F.R. § 1.132 Declaration of Hiroshi Takeyama filed 4/14/2006, the Examiner is not persuaded that the results are a) unexpected and b) commensurate in scope with the claims. Specifically, there is no evidence of unexpected synergy over the broad range of doses and ratios instantly claimed. To this point, the first set of results presented in the Declaration (page 2; Figure 1) show that a dose of 116.4, 232.8, 465.5, and 931 μg/mL benzyl alcohol administered to STKM stomach cancer cells *in vitro* results in a decrease in the adhesive property of the cells and death of the cells. A change in adhesive property and cell death was not observed in concentrations of 50 μg/mL. In the second set of results (page 4), benzyl alcohol and vitamin C were combined in concentrations ranging from 10,000 μg/mL benzyl alcohol + 100,000 μg/mL vitamin C to 4.9 μg/mL benzyl alcohol + 49 μg/mL vitamin C. In all cases, the ratio of benzyl alcohol to vitamin C was 1:10. However, the claims recite ratios of 10:1 to 1:10

benzyl alcohol to vitamin C (*i.e.*, "...wherein vitamin C is used in a range of 0.1 to 10 times per 1 part of benzyl alcohol by weight..."). Further, all that is stated in the Declaration is that the adhesive property of the cells decreased and cell death increased when benzyl alcohol and vitamin C were administered; in other words, the same result that is seen with benzyl alcohol alone. There is no comparison to cells treated with only vitamin C. Neither is there a direct comparison of cells treated with the same dose of benzyl alcohol, both alone and in combination with vitamin C. Accordingly, the Examiner cannot accept the experimental results presented in the Declaration as evidence of an "unexpected" result.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1-3 and 16-17 are rejected under 35 U.S.C. § 103(a) as being unpatentable over "The antitumor effect to stomach cancer by benzyl alcohol," Meeting of Japan Surgical Society on April 12-14, 2000, issued on March 10, 2000, PP-1457 (listed on PTO Form 1449, dated October 27, 2003, with a translation provided by Applicant), hereafter referred to as "Reference PP- 1457" and Head, K.A. (Alternative Medicine Review, 1998, vol. 3, no. 3, pages 174-186) (newly cited) in view of Casciari *et al.* (U.S. Patent No. 6,448,287 B1; Issued 9/10/2002) (prior art of record).

The instant claims recite a method of treating a stomach tumor comprising administering benzyl alcohol at a dose of 1 to 50 mg/cm^3 of tumor volume in combination with vitamin C in a range of 0.1 to 10 times per 1 part benzyl alcohol.

Reference PP-1457 teaches administration of 200, 300, 400, 500, and 1000 μg benzyl alcohol to cells of the stomach cancer cell line STKM ("Method"). 300 μg or more of benzyl alcohol resulted in "mortality" of the STKM cells ("Result"). The apoptosis induced by benzyl alcohol in the stomach cancer cell line *in vitro* was induced by 1/3000 of the maximum permissible dose in a human, thus suggesting and motivating higher doses ("Consideration"). The reference further suggests that further *in vivo* testing is required and that benzyl alcohol may be used as an anti-tumor agent, thus motivating in vivo treatment of stomach tumors (*id.*). With respect to "external administrating" as recited in instant claim 2, adding the benzyl alcohol to the cultured cells in their dish would include externally administering the composition; in other words, the reference does disclose application of the benzyl alcohol directly onto the cells. The reference also indicated:

Since we found out that Benzyl alcohol had antitumor effect to a stomach cancer, we report said effect herein.

which, absent factual evidence to the contrary would suggest *in vivo* treatment and since the gut space is "external" to the body, would have been anticipated as a method of external administration. The reference does not teach or suggest administering benzyl alcohol in combination with vitamin C for the treatment of stomach tumors.

However, Head reviews the use of ascorbic acid (*i.e.*, vitamin C) in the prevention and treatment of cancer. Proposed mechanisms of action for ascorbic acid in the prevention and treatment of cancer include enhancement of the immune system, stimulation of collagen formation necessary for "walling off" tumors, inhibition of hyaluronidase which prevents metastasis, prevention of oncogenic viruses, enhancement of the effect of certain chemotherapeutic drugs, prevention of free radical damage, and neutralization of carcinogenic substances (Abstract). Head reviews several clinical studies on the use of vitamin C in the treatment of cancer patients (pages 176-180), including the instantly claimed stomach cancer (Table 1). In conclusion, Head suggests that while vitamin C alone may not be enough of an intervention in the treatment of most active cancers, since it appears to improve quality of life and extend survival time, it should be considered as a part of a treatment protocol for all patients with cancer (page 184). The reference thus suggests and motivates the addition of vitamin C to existing chemotherapy regimens.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

In the absence of s showing of unexpected results commensurate in scope with the claims, the instantly claimed method of treating stomach tumors with benzyl alcohol and vitamin C would have been *prima facie* obvious at the time the invention was made. Benzyl alcohol was known to be effective in inducing apoptosis of stomach cancer cells at doses of 200, 300, 400, 500, and 1000 μg. Vitamin C has shown efficacy in the treatment of numerous cancers in human patients, including the instantly claimed stomach cancer and is further suggested as an additive to existing treatment protocols. As such, one skilled in the art would have been imbued with at least a reasonable expectation that the combination of benzyl alcohol and vitamin C would be effective in treating stomach tumors. With respect to the claimed dose of benzyl alcohol (*i.e.*, 1 mg to 50 mg/cm^3 tumor volume) and amount of vitamin C (0.1 to 10 times per 1 part benzyl alcohol), such amounts are not seen as inventive over the prior because they would have been elucidated *via* routine dosing optimization. In this regard, Casciari *et al.* is provided as evidence that vitamin C can be administered in a ratio of 1:1 to 3500:1, preferably 10:1 to 100:1 with another drug (col. 2, lines 15-19).

Accordingly, the claims are deemed properly rejected because the prior art teaches that benzyl alcohol is effective in the treatment of stomach tumors and further suggests that vitamin C should be used as a part of treatment for all patients with cancer.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Patent Examiner
AU 1614

December 4, 2007

12/8/07

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER